Only three tappings of the abdomen were necessary after commencing the diet, and the oedema of the legs, thighs, scrotum, and penis gradually subsided; the lumbar cushion also disappeared. A marked loss of weight, due no doubt to the elimination of fluid, was later succeeded by a steady gain as nutrition improved. Nothing could be more satisfactory than the way in which the fluid which waterlogged this patient was induced to disperse. His subsequent history is, however, well worth noting. It is over a twelvemonth since his last tapping. He continues his diet on much the same lines, remains free from ascites and oedema, has put on flesh and looks and feels much better, but his urine is still highly albuminous, and his blood pressure has gradually risen until the systolic pressure is 220 mm. of mercury.

There can be no doubt that the institution of a diet on Epstein's lines was completely successful in restoring this man to a condition of comfort when the ordinary means of treatment combined with salt deprivation had failed. Now, Epstein, as a result of his investigations on renal disease, came to the conclusion that the amount of protein in the blood was very seriously diminished in chronic parenchymatous nephritis, and that this diminution was the direct result of the loss of albumin in the urine. As the result of this there is a diminution in the osmotic pressure of the blood—that is, of the power of the blood to attract fluid from the tissues—a state of affairs which favours the imbibition and retention of fluid by the tissues themselves. Thus he accounts for the oedema and serous effusions met with in chronic parenchymatous nephritis, a form of renal disease in which it is well known that albuminuria is profuse.

Before specifying his diet another point has to be mentioned: Not only did he find blood protein deficient in these cases, but he also detected a remarkable increase in the lipoid—that is to say, the cholesterin content of the blood, which he attributed to the mobilization of the fatty deposits in the body, and perhaps also to tissue degeneration. Epstein's diet, therefore, is rich in protein and poor in fat to meet these conditions.

EPSTEIN'S DIET.

The daily food value is from 1,280 to 2,500 calories.
Protein from 120 to 240 grams.
Fat (unavoidable) 20 to 40 grams.
Carbohydrates 150 to 300 grams.
The articles used are lean veal, lean ham, whites of eggs, oysters, gelatin, Lima beans, lentils, split peas, green peas, mushrooms, rice, oatmeal, bananas, skimmed milk, coffee, tea, and cocoa.
Of fluid, 1,200 to 1,500 c.cm. are allowed, and the amount of salt is in quantity sufficient to make the food palatable.

Fortunately, at the time when this patient was in St. Thomas's Hospital, Drs. MacLean and De Wesselow were already engaged in their investigation on war nephritis which is being carried on there, and I obtained their ready assistance for the investigation of my case.

Two striking facts emerged: first, during the period of diuresis the already low protein content of the blood plasma tended rather to diminish than to increase; secondly, the urea content of the blood became augmented. The actual figures were as follows:

| Date. | Protein in Blood Plasma. | Urea in Blood. |
|---|---|---|
| | Per cent. | |
| October 13th, 1918 ... ... | 6.29 | 27 mg. per 100 c.cm. |
| November 20th, 1918 ... ... | 6.20 | 64 mg. per 100 c.cm. |
| December 3rd, 1918 ... ... | 6.00 | 56 mg. per 100 c.cm. |
| January 3rd, 1919 ... ... | — | 81 mg. per 100 c.cm. |
| January 22nd, 1919 ... ... | 5.96 | 63 mg. per 100 c.cm. |

These results led Dr. MacLean to infer that, in this instance at all events, Epstein's explanation of the disappearance of the dropsical effusions could not apply, and that the diuresis and consequent disappearance of the effused fluid from the subcutaneous tissues and the serous sacs which resulted from the adoption of the rich protein diet was to be attributed, not to an increased richness of the blood in protein, but to an increase in its urea content, which rose from 27 mg. per 100 c.cm. at the beginning of the new diet to an average of about 60 mg. per 100 c.cm. Urea is known to be a powerful diuretic, and the administration of fairly large doses of urea to patients who suffer from renal oedema has been found to set up a diuresis similar to that which occurred in the case just narrated.

Whether patients who are the subjects of oedematous renal disease can be injured by the adoption of the high protein diet is a question which calls for serious consideration. The institution of such a diet does not appear to increase in any appreciable degree the amount of albumin which is being lost by the kidneys, and which in itself must be a serious drain, but, as we have seen, it does undoubtedly increase the amount of urea, and presumably also the other non-protein nitrogenous bodies, in the blood. The administration of urea in large doses occasionally induces headache, but apparently, in healthy persons at all events, has no appreciable effect in raising the blood pressure. My patient, although free from oedema and serous effusions and making no complaint of headache or other discomfort, shows a gradually increasing blood pressure, which at the last observation has reached 220 mm. of mercury. It is tempting to associate this rise of pressure with the retention of the non-protein nitrogenous substances in the blood, and it is important to determine whether increased blood pressure is the usual sequel of a rich protein diet in such cases. There is some reason to suspect that it is.

At the same time it is well to bear in mind that patients with large white kidneys who survive the oedematous stage are described as passing into a condition comparable to that induced by contracted granular kidneys—that is to say, a condition in which increasing polyuria is associated with pronounced cardio-vascular changes. It might well be urged, therefore, that the present condition of my patient is but the natural result of the evolution of his disease. Whatever be the explanation, the fact remains that the adoption of the high protein diet enables these patients to survive the waterlogged stage and its associated dangers, a survival which experience has shown was rare before this type of diet was adopted.

As regards diet in *acute* nephritis we remain much where we were. A low protein supply is obviously indicated in the early stage of the disease owing to the presence of urea retention. Should dropsy be present, it is also advisable to restrict or eliminate salt, and not to allow *excessive* ingestion of fluids. The old warning against beef-tea and meat extracts is justified since they are rich in both salt and nitrogenous derivatives, whilst the idea that toxic products might be eliminated by considerably increasing the fluid intake is not supported by what we know about the mechanism of the oedema. Milk still remains our staple article of food at this stage, not because it is a non-nitrogenous diet, which it assuredly is not, but because it is easily assimilated, slightly diuretic, and by experience found to be least harmful. When the acute stage is passed, a rather more liberal protein diet appears to do no harm. The addition of some protein to the carbohydrates usually allowed at this stage does not appear to increase the albumin or produce other harmful effects.

As to chronic nephritis of the hydraemic type, Epstein's diet certainly affords slow and steady relief to the dropsical symptoms, but the ultimate outcome is still *sub judice*, whilst in that form of which the granular kidney is the type and urea retention the rule, the established treatment by reducing the protein and extractives is fully corroborated.

## THE LIFE-HISTORY OF THE FIRST CASE OF MYXOEDEMA TREATED BY THYROID EXTRACT.

BY GEORGE R. MURRAY, M.D., D.C.L., F.R.C.P.,
PROFESSOR OF SYSTEMATIC MEDICINE IN THE VICTORIA UNIVERSITY, AND PHYSICIAN TO THE ROYAL INFIRMARY, MANCHESTER; LATELY COLONEL A.M.S. AND CONSULTING PHYSICIAN IN ITALY.

THE development of the principles and practice of endocrinology during the last thirty years has been rapid and progressive. The practice of this branch of medicine has unfortunately not always been based on sound physiological principles, so that glandular extracts have been given indiscriminately in many conditions with disappointing results. In the case of some preparations there is little evidence that the hormones they are supposed to contain are able to exert their normal physiological action when given by the mouth. It therefore may be

of interest to complete the life-history of the first case of myxoedema successfully treated by thyroid extract—it has recently terminated at the age of 74—as the results obtained in this case not only afforded definite proof that the thyroid gland produced an internal secretion, but showed that the thyroidal insufficiency of myxoedema in man could be made good by maintaining an adequate supply of thyroidal hormones from an external source.

During the war we learned to appreciate more fully the value of the collective investigation of disease for which the aggregation of large numbers of men under military discipline and the co-operation of groups of medical officers provided the opportunity. A striking example of the results to be obtained by this method had, however, already been furnished by the publication, in 1888, of the report of the special committee which was appointed by the Clinical Society[1] in 1883 to investigate the relation of myxoedema and allied conditions to the thyroid gland. The history of the subsequent developments of the treatment of these maladies as a direct result of the work of this committee has just been so clearly given by Mr. Stephen Paget[2] that further reference to it is not necessary. It is, of course, well known that the experimental work of Sir Victor Horsley, which was undertaken at the request of this committee, first definitely proved that myxoedema, cretinism, and cachexia strumipriva were due to loss of function of the thyroid gland. Although at that time it had not been proved that this function was to provide an internal secretion, he suggested that grafting a portion of healthy thyroid gland would be a rational method of treating these maladies.[3] The striking improvement which followed the adoption of this suggestion in Bettencourt and Serrano's[4] case led me to suggest and carry out the treatment of myxoedema by thyroid extract in the case whose complete life-history I now wish to record as an example of the value of observation of individual cases over long periods of time in the elucidation of certain problems in medicine.

Mrs. S., aged 46, was shown at a meeting of the Northumberland and Durham Medical Society on February 12th, 1891.[5] She had had a family of nine children, of whom six were living. At the age of 40 she had a miscarriage, after which she had menstruated once, at the age of 42. When she was 41 or 42 years of age her relations had noticed that she was becoming slow in speech and action, and she herself began to find that it required a great effort to carry on her ordinary housework. The features gradually became enlarged and thickened and the hands and feet increased in size and changed in shape, so that at the time of this meeting she presented the typical features of an advanced case of myxoedema of at least four years' duration. After showing the patient, I stated my intention of treating her with thyroid extract, and described the principles upon which this treatment was based and the reasons for expecting that it would be successful. The treatment was not commenced until two months later, and the following note taken on April 13th, 1891, describes her condition at that time:

> She complains of languor, a disinclination to see strangers, and great sensitiveness to cold. The temperature is subnormal, and varies between 95.6° and 97.2° in the mouth. The pulse varies between 60 and 70. The face is blank and expressionless and the features are notably thickened. This change is well seen in the alae nasi and lips. The subcutaneous connective tissue of the eyelids is so swollen that she finds it difficult to look upwards. There is also considerable swelling beneath the eyes and of the cheeks. The hands and feet are both enlarged; the former have that peculiar shape which has been described as spade-like. The skin is very dry, there is no perspiration, and the superficial layers of the epidermis are continually being shed as a fine white powder. The hair is very fine in texture, and a considerable quantity of it has been lost. She is slow in answering questions; all her actions are slow and are performed with difficulty. The speech is remarkably slow and drawling and the memory is bad. No thyroid gland can be felt in the neck. The urine contains no albumin or sugar.

The experimental nature of the treatment was explained, and the patient, realizing the otherwise hopeless outlook, promptly consented to its trial. In order to ensure that the extract was properly prepared, the thyroid gland was removed from a freshly killed sheep with sterilized instruments and conveyed at once in a sterilized bottle to the laboratory where the glycerin extract was prepared, as elsewhere described.[6] This extract was afterwards included in the *British Pharmacopoeia* of 1898 as "liquor thyroidei."

At that time care in obtaining the actual thyroid gland was necessary, as was shown by the experience of the late Dr. Michell Clarke, who, in the course of a discussion on a paper read by me at the annual meeting of the British Medical Association at Nottingham in 1892,[7] stated that he had carried out the treatment without any benefit in two cases. Several years later Dr. Clarke kindly told me he had subsequently discovered that his want of success was due to the fact that the butcher had been supplying thymus instead of thyroid gland for the preparation of the extract. Even in recent years some thyroid preparations have proved to be inactive. In the treatment of this first case a hypodermic injection of 25 minims of the extract was given twice a week at first, and later on at longer intervals. The patient steadily improved, and three months later, on July 13th, the condition was thus described:

> The swelling has gradually diminished, and has practically disappeared from the backs of the hands, the skin over them being now loose and freely movable. The lips are much smaller. The swelling of the upper eyelids has diminished so much that she can look upwards quite easily. The swelling beneath the eyes and of the cheeks has also much diminished. The face consequently, as a whole, has greatly improved in appearance and has much more expression, as many of the natural wrinkles, especially about the forehead, have returned. The speech has become more rapid and fluent, the drawl being scarcely noticeable at the present time. She answers questions much more readily, the mind has become more active, and the memory has improved. She is more active in all her movements, and finds that it requires much less effort than formerly to do her housework. She now walks about the streets without any hesitation without a companion.
>
> She has menstruated normally during the last six weeks at the regular interval. For the last four weeks the skin has been much less dry and she perspires when walking. The hair remains as before. She is no longer so sensitive to cold. Unfortunately owing to circumstances a daily record of the temperature has not been kept, but out of four observations that have been made lately, about 11 a.m., three times the temperature has been 98.2° F. and once 97.4.°

After this the injections were given at fortnightly intervals, and later on, when the oral administration had been shown by Dr. E. L. Fox and Dr. Hector Mackenzie[8] to be equally efficient, she took 10 minims by the mouth six nights a week, so that 1 drachm was consumed in the course of each week. On this dose she remained in good health, and free from the signs of myxoedema. I have only seen this patient once during the last eleven years, but Dr. Helen Gurney, medical registrar at the Royal Victoria Infirmary, Newcastle, has kindly kept her under observation, and has informed me that she continued to take liquid thyroid extract regularly until early in 1918, when it became difficult to obtain, so that she was given dry thyroid extract in a tablet instead. She enjoyed excellent health until early in 1919, when she developed oedema of the legs, and died in May of that year at the age of 74 from cardiac failure.

This patient was thus enabled, by the regular and continued use of thyroid extract, to live in good health for over twenty-eight years after she had reached an advanced stage of myxoedema. During this period she consumed over nine pints of liquid thyroid extract or its equivalent, prepared from the thyroid glands of more than 870 sheep.

The results obtained in this case show that:

1. The thyroid is purely an internal secretory gland.
2. The symptoms of myxoedema can be entirely removed, and the patient maintained in good health, by the continuous administration of thyroid extract.
3. The functions of this gland in man can be fully and permanently carried on by the continued supply of thyroidal hormones obtained from one of the lower animals.
4. The duration of life need not be shortened by atrophy of the thyroid gland provided this substitution treatment is fully maintained, and so under these circumstances the prognosis of myxoedema is very good.


REFERENCES.

[1] Clinical Society's *Transactions*, Supplement to vol. xxi. [2] *Sir Victor Horsley: A Study of His Life and Work*, by Stephen Paget, pp. 52-67. [3] BRITISH MEDICAL JOURNAL, February 8th, 1890, p. 287. [4] *La Semaine Médicale*, August 13th, 1890. [5] *Transactions* of the Northumberland and Durham Medical Society, February, 1891. [6] BRITISH MEDICAL JOURNAL, October 10th, 1891. [7] Ibid., August 27th, 1892. [8] Ibid., October 29th, 1892.